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sFlt-1 and NTproBNP independently predict mortality in a cohort of heart failure patients.

Melinda A. Paterson[1], Anna P. Pilbrow[1], Chris M. Frampton[1], Vicky A. Cameron[1], Chris J. Pemberton[1], Mayanna Lund[2], Gerard P. Devlin[3], Robert N. Doughty[4], A. Mark Richards[1,6], Barry R. Palmer[1,5]

[1]Christchurch Heart Institute, Department of Medicine, University of Otago Christchurch, [2]Cardiology Department, Middlemore Hospital, Auckland, [3]Department of Cardiology, Waikato District Health Board, Hamilton, [4]Department of Medicine, Faculty of Medicine and Health Sciences, University of Auckland, Auckland, [5]School of Health Sciences, College of Health, Massey University, Wellington, New Zealand and [6]Cardiovascular Research Institute, National University of Singapore, Singapore

Background

- Heart failure is a common and important form of heart disease in New Zealand with a high mortality rate.
- The Prospective Evaluation of Outcome in Patients with Heart Failure with Preserved Left Ventricular Ejection Fraction (PEOPLE) study is a prospective study of representative patients with validated HF from four New Zealand hospitals. (1)
- This study investigated baseline levels of sFlt-1, a receptor for VEGF-A that circulates in plasma, as a prognostic marker in heart failure patients using samples from the PEOPLE cohort. (2-4)
- The VEGF system, including VEGF-A and sFlt-1, stimulate the production of new blood vessels, including collateral circulation, which is known to improve heart function. (5,6)
- NTproBNP is the established plasma marker for diagnosis of heart failure and is a strong prognostic predictor of clinical outcome in heart failure patients (7).

Methods

ELISA assays for sFlt-1 and NTproBNP were performed in n=858 patients from the PEOPLE study of outcome among patients after appropriate treatment for an episode of acute decompensated HF in New Zealand. Plasma was sampled at a baseline visit and stored at -80°C.

Results

- Mean baseline plasma sFlt-1 levels was 125 ± 2.01 pg/ml.
- sFlt-1 was higher in patients with HF with reduced ejection fraction (HFrEF) (130 ± 2.62 pg/ml, n=553) compared to those with HF with preserved EF (HFpEF) (117 ±3.59 pg/ml, n=305; p=0.005) (Figure 1).
- sFlt-1 correlated with heart rate (r=0.148, p<0.001), systolic blood pressure (r=-0.139, p<0.001) and LVEF (r=-0.088, p=0.019).
- Above median levels of sFlt-1 were associated with increased mortality (p<0.001) (Figure 2).
- Multivariate analysis using a Cox proportional hazards model showed sFlt-1 was a predictor of all-cause death (HR=6.30, p<0.001) in the PEOPLE cohort, independent of age, NTproBNP, ischaemic aetiology, and NYHA class (n=842; 274 deaths) and other established predictors of mortality in the PEOPLE cohort (Table 1).

Table 1.

Cox's proportional hazards regression model for mortality in the PEOPLE cohort (n=842; 274 deaths).

	df	Significance	Hazard Ratio	95% CI for HR	
				Lower	Upper
NYHA class	3	0.365			
NYHA I versus IV	1	0.342	0.765	0.441	1.329
NYHA II versus IV	1	0.711	0.919	0.587	1.439
NYHA III versus IV	1	0.195	0.743	0.475	1.164
Age	1	0.001	1.019	1.008	1.031
Log10 sFlt1	1	0.021	2.671	1.163	6.133
Log10 NT-proBNP	1	< 0.001	1.359	1.195	1.547
Creatinine	1	0.044	1.002	1.000	1.005
Gender	1	0.018	0.843	0.732	0.971
Beta-Blocker at discharge	1	0.006	1.46	0.522	0.895
Antecedent Hypertension	1	0.071	0.885	0.99	1.29
Antecedent diabetes	1	0.014	0.848	1.03	1.29

Figure 1a.

Comparison of baseline sFlt-1 levels in the subgroups of the PEOPLE cohort defined by preserved and reduced ejection fraction (mean +/- standard error).

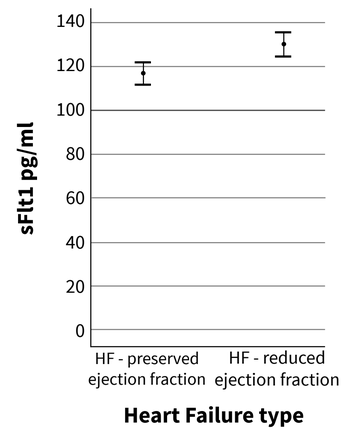


Figure 1b.

The Vascular Endothelial Growth Factor (VEGF) System. sFlt-1 acts as a decoy receptor, reducing the binding of VEGF to membrane-bound Flt-1 and KDR, down-regulating stimulation of angiogenesis.
Drawn by Tom Wilkinson.

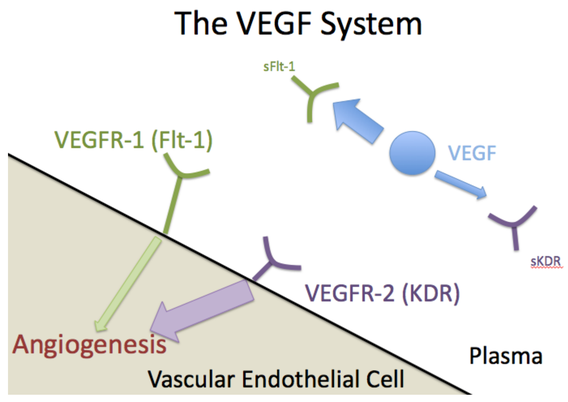
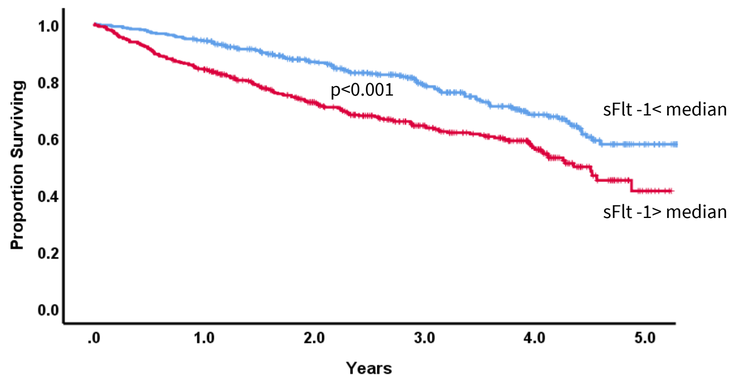


Figure 2.

Kaplan-Meier survival curve of the PEOPLE cohort stratified by above and below median baseline sFlt-1 levels.



							Events
sFlt-1 below median	435	404	301	193	102	18	112 (25.7%)
sFlt-1 above median	423	349	253	161	89	8	166 (39.2%)

Conclusion

sFlt-1 levels at baseline should be investigated further as a predictor of death, complementary to established prognostic biomarkers in heart failure.

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Paterson, MA

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